Jazz Pharmaceuticals Presents Data Highlighting the Continued Need for Low-Sodium Treatment Option Xywav® (calcium, magnesium, potassium, and sodium oxybates) Oral Solution and Real-World, Evidence-Based Approaches for Individualized Treatment in Adults with Narcolepsy at World Sleep 2023

October 23, 2023

Two presentations focus on cardiovascular disease risk among patients with sleep disorders and the impact of sodium intake on cardiometabolic comorbidities, highlighting the need for low-sodium treatment options

TENOR study findings show that the most common patient-reported reasons for utilizing a Xywav individualized dosing regimen were to avoid morning grogginess, help fall asleep and improve sleep quality

DUBLIN, Oct. 23, 2023 /PRNewswire/ -- Jazz Pharmaceuticals plc (Nasdaq: JAZZ) today announced new data that examine the comorbid risk of cardiovascular disease in patients with narcolepsy and idiopathic hypersomnia as well as the effect of sodium intake on cardiovascular health. The Company will also present results from the real-world TENOR study on individualized dosing regimens for adults with type 1 or type 2 narcolepsy transitioning to low-sodium Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution from high-sodium Xyrem® (sodium oxybate) oral solution. The study will be presented today at the World Sleep 2023 Congress in an oral session on evidence-based approaches for optimizing pharmacologic treatment for narcolepsy.

Xywav is the first and only low-sodium oxybate approved in the U.S. for the treatment of cataplexy or excessive daytime sleepiness in patients 7 years of age and older with narcolepsy and for the treatment of idiopathic hypersomnia in adults. *Xywav* contains the same active moiety as *Xyrem*, but the maximum recommended nightly dose contains only 131 mg of sodium, which is 92% less sodium than the 1,640 mg of sodium contained in the maximum recommended nightly dose of *Xyrem*. At the maximum recommended dose, the sodium content in *Xyrem* equates to 109% of the American Heart Association's daily ideal sodium intake for most adults, while the sodium content in *Xywav* accounts for less than 10% of this standard. This substantial reduction could allow patients switching from *Xyrem* to *Xywav* to achieve a daily sodium intake target of 2,300 mg, and ideally 1,500 mg, as set by the American Heart Association.[1]

Two presentations underline the importance of low-sodium treatment options to help manage cardiovascular risk in patients with narcolepsy and idiopathic hypersomnia:

- An exploratory, post-hoc analysis from two Phase 3 trials of *Xywav* in narcolepsy and idiopathic hypersomnia examined changes in blood pressure among patients previously naïve to oxybate therapy. At baseline, the mean systolic blood pressure, measured in millimeters of mercury (mmHg), was 122.1 mmHg and 122.8 mmHg in patients with narcolepsy and idiopathic hypersomnia, respectively. The analysis found that there were no clinically meaningful differences from baseline in systolic blood pressure in those who initiated treatment with low-sodium *Xywav* during the 10- to 14-week open-label study periods.
- A separate presentation on findings from a systematic review of literature evaluating the relationship between sodium intake and clinical outcomes demonstrated some statistically significant associations between higher sodium intake and certain cardiovascular and cardiometabolic outcomes.

These studies demonstrate that low-sodium therapies, in addition to comprehensive management plans focusing on the holistic health of patients, can help patients with narcolepsy and idiopathic hypersomnia reduce their chronic sodium burden. This reduction in sodium burden further contributes to the mitigation of certain health risks in patients with sleep disorders, who have an increased risk of cardiovascular and cardiometabolic morbidity based on their diagnosis.

"Narcolepsy and idiopathic hypersomnia impact day-to-day functioning across settings, and moreover, are linked with a significantly increased occurrence of a broad range of cardiovascular comorbidities," said Kelvin Tan, MB BCh, MRCPCH, senior vice president, chief medical officer, Jazz Pharmaceuticals. "These data suggest that clinicians should carefully monitor the cardiovascular health of their patients with sleep disorders, discuss modifiable risk factors such as sodium intake and consider prescribing therapies that take their cardiovascular risk into account."

In addition, the prospective, observational **T**ransition **E**xperience of Persons With **N**arcolepsy Taking **O**xybate in the **R**eal-World or TENOR study will be shared as an oral presentation today. As defined, individualized dosing applies to twice-nightly oxybates, including *Xyrem* and *Xywav*, and encompasses the following to achieve an optimal treatment experience: the ability to titrate with precision down to 0.25 mg, the ability to adjust the timing of the 2nd dose to occur between 2.5-4 hours after the 1st dose and the ability to prescribe equal or unequal doses for the 1st and 2nd doses. In the analysis, 20% (n=17/85) of patients reported benefiting from individualized dosing, specifically taking unequal doses (narcolepsy type 1, n=7; narcolepsy type 2, n=10) at any point, with 12% (8/85) of patients reporting they were taking an unequal dosing regimen at 21 weeks. Overall, the most common reasons cited for taking a higher first dose were to avoid feeling groggy in the morning (44% and 33%, respectively), to help fall asleep (25% and 13%, respectively), and to improve sleep quality (13% and 29%, respectively). These real-world insights may help inform clinical decision-making around individualizing dosing regimens in patients with narcolepsy.

"Real-world data regarding individualized dosing regimens for the treatment of narcolepsy are limited. As an established leader in sleep medicine, we are committed to helping patients find effective approaches to manage this chronic, debilitating sleep disorder," said Wayne Macfadden, MD, sleep therapeutic area lead, neuroscience global medical affairs, Jazz Pharmaceuticals. "The real-world insights revealed in the TENOR study may help

healthcare providers counsel patients with narcolepsy around dosing regimens to meet their individual needs and goals for improved daytime functioning. An individualized approach to *Xywav* dosing would not only empower patients to communicate their goals and unique needs, but also enable healthcare providers to adapt more effectively, helping to advance improved patient outcomes."

The TENOR study was a patient-centric, prospective, observational study of U.S. adults with type 1 or type 2 narcolepsy. In the study, 85 patients (narcolepsy type 1, n=45; narcolepsy type 2, n=40) transitioning to low-sodium *Xywav* from high-sodium *Xyrem* completed daily and weekly diaries and questionnaires for 21 weeks post-transition.

About Narcolepsy
Narcolepsy is a chronic, debilitating neurologic sleep disorder characterized by excessive daytime sleepiness (the inability to stay awake and alert during the day resulting in the irrepressible need to sleep or unplanned lapses into sleep or drowsiness), or EDS, and an inability to regulate sleep-wake cycles normally.[2] Patients with EDS due to narcolepsy experience sleep attacks and, despite fighting the urge to sleep, may unintentionally fall asleep for short periods.[3,4] These sleep attacks may happen at inappropriate or potentially dangerous times such as during driving, cycling, eating or mid-conversation.[5]

There is no cure for narcolepsy, therefore EDS is lifelong and has a substantial negative impact on a person's ability to function psychologically, socially and professionally.[6] Patients with narcolepsy are at increased risk for hypertension, cardiometabolic morbidity, stroke, myocardial infarction, heart failure, cardiac arrest and death.[7,8,9,10] As narcolepsy is a chronic condition that requires lifelong, nightly treatment, early access to an effective, low-sodium treatment can transform lives and reduce a patient's cardiovascular risk.[6]

About Idiopathic Hypersomnia
Idiopathic hypersomnia is a distinct, neurologic sleep disorder that goes beyond chronic excessive daytime sleepiness (EDS).[11,12,13,14] Idiopathic hypersomnia occurs in a unrelenting 24-hour cycle, and symptoms may include a prolonged but non-restorative nighttime sleep episode of more than 9 hours, or a 24-hour sleep duration of 11 hours or longer, profound sleep inertia (prolonged difficulty waking, with frequent reentries into sleep, confusion, and irritability), cognitive impairment, long and unrefreshing naps and EDS that persists throughout the day. [11,12,13,14,15] Although there are overlapping clinical features with narcolepsy, idiopathic hypersomnia is a condition with its own specific diagnostic criteria.[14,16]

Idiopathic hypersomnia is a debilitating illness that can severely limit patients' occupational, familial and social functioning.[17,18] In the U.S., approximately 37,000 adult patients have been diagnosed with idiopathic hypersomnia and are actively seeking healthcare.[19] This low number of people may be due to the many difficulties in identifying and diagnosing idiopathic hypersomnia, as well as distinguishing it from other similar sleep disorders. It is estimated that far fewer patients are currently receiving pharmacological treatment for their idiopathic hypersomnia.[19,20,21,22]

About Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution
Xywav is a low-sodium oxybate approved by the U.S. Food and Drug Administration (FDA) for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy. The FDA recognized seven years of Orphan Drug Exclusivity for *Xywav* in June 2021 for the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy. The Office of Orphan Product Development (OOPD) at the FDA also published its summary of clinical superiority findings for *Xywav* for the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy by means of greater cardiovascular safety compared to Xyrem® (sodium oxybate) oral solution. The decision of the OOPD is based on the FDA findings that *Xywav* provides a greatly reduced chronic sodium burden compared to *Xyrem*. *Xywav* has 131 mg of sodium at the maximum recommended nightly dose. *Xywav* is comprised of a unique composition of cations resulting in 92% less sodium, or a reduction of approximately 1,000 to 1,500 mg/night. *Xywav* is the only low-sodium oxybate therapy approved by the FDA, and the only oxybate that does not carry a warning in the label related to high sodium intake.

Xywav is also the first and only U.S. FDA-approved treatment option for idiopathic hypersomnia in adults. The FDA recognized seven years of Orphan Drug Exclusivity for *Xywav* in December 2021 for the treatment of idiopathic hypersomnia in adults. *Xywav* is the only FDA-approved treatment studied across the multiple symptoms of idiopathic hypersomnia, such as EDS, sleep inertia (severe grogginess or confusion when waking up), long sleep duration and cognitive impairment. *Xywav* can be administered as a twice- or once-nightly regimen for the treatment of idiopathic hypersomnia in adults.

The exact mechanism of action of *Xywav* in the treatment of adults with idiopathic hypersomnia and of cataplexy and EDS in narcolepsy is unknown. It is hypothesized that the therapeutic effects of *Xywav* are mediated through $GABA_B$ actions during sleep at noradrenergic and dopaminergic neurons, as well as thalamocortical neurons.[23] The U.S. Drug Enforcement Agency (DEA) has designated *Xywav* as a Schedule III medicine. The DEA defines Schedule III drugs, substances, or chemicals as drugs with a moderate to low potential for physical and psychological dependence.[23,24] Because of the risks of central nervous system (CNS) depression and abuse and misuse, *Xywav* is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the XYWAV and XYREM REMS.

Important Safety Information for Xywav

WARNING: Taking XYWAV with other central nervous system (CNS) depressants such as medicines used to make you or your child fall asleep, including opioid analgesics, benzodiazepines, sedating antidepressants, antipsychotics, sedating anti-epileptic medicines, general anesthetics, muscle relaxants, alcohol, or street drugs, may cause serious medical problems, including trouble breathing (respiratory depression), low blood pressure (hypotension), changes in alertness (drowsiness), fainting (syncope), and death.

The active ingredient of XYWAV is a form of gamma-hydroxybutyrate (GHB). Abuse or misuse of illegal GHB alone or with other drugs that cause changes in alertness (or consciousness) has caused serious side effects. These effects include seizures, trouble breathing (respiratory depression), changes in alertness (drowsiness), coma, and death. Call your doctor right away if you or your child has any of these serious side effects.

Because of these risks, you have to go through the XYWAV and XYREM REMS to have your or your child's prescription for XYWAV filled.

Do not take XYWAV if you take or your child takes other sleep medicines or sedatives (medicines that cause sleepiness), drinks alcohol, or has a rare problem called succinic semialdehyde dehydrogenase deficiency.

Keep XYWAV in a safe place to prevent abuse and misuse. Selling or giving away XYWAV may harm others, and is against the law. Tell your doctor if you have ever abused or been dependent on alcohol, prescription medicines, or street drugs.

Anyone who takes XYWAV should not do anything that requires them to be fully awake or is dangerous, including driving a car, using heavy machinery, or flying an airplane, for at least 6 hours after taking XYWAV. Those activities should not be done until you know how XYWAV affects you or your child.

XYWAV can cause serious side effects, including the following:

- **Breathing problems, including** slower breathing, trouble breathing, and/or short periods of not breathing while sleeping (sleep apnea). People who already have breathing or lung problems have a higher chance of having breathing problems when they use XYWAV.
- **Mental health problems, including** confusion, seeing or hearing things that are not real (hallucinations), unusual or disturbing thoughts (abnormal thinking), feeling anxious or upset, depression, thoughts of killing yourself or trying to kill yourself, increased tiredness, feelings of guilt or worthlessness, or difficulty concentrating. Tell your doctor if you or your child have or had depression or have tried to harm yourself or themselves. **Call your doctor right away if you have or your child has symptoms of mental health problems or a change in weight or appetite.**
- **Sleepwalking.** XYWAV can cause sleepwalking, which can cause injuries. Call your doctor if this occurs.

The most common side effects of XYWAV in adults include nausea, headache, dizziness, anxiety, insomnia, decreased appetite, excessive sweating (hyperhidrosis), vomiting, diarrhea, dry mouth, parasomnia (a sleep disorder that can include abnormal dreams, abnormal rapid eye movement (REM) sleep, sleep paralysis, sleep talking, sleep terror, sleep-related eating disorder, sleep walking, and other abnormal sleep-related events), somnolence, fatigue, and tremor.

The most common side effects of XYREM (which also contains oxybate like XYWAV) in children include nausea, bedwetting, vomiting, headache, weight decrease, decreased appetite, dizziness, and sleepwalking.

XYWAV can cause physical dependence and craving for the medicine when it is not taken as directed. These are not all the possible side effects of XYWAV.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please see full Prescribing Information, including Boxed Warning, here: https://pp.jazzpharma.com/pi/xywav.en.USPI.pdf

About Xyrem® (sodium oxybate) oral solution
Xyrem oral solution, CIII, is a product approved by the U.S. Food and Drug Administration (FDA) for both cataplexy and excessive daytime sleepiness in narcolepsy in adult and pediatric patients ages 7 and older.[25] *Xyrem* may only be dispensed to patients enrolled in the XYWAV and XYREM REMS. *Xyrem* was first approved in the U.S. in 2002, based on clinical trial data in adults.

Important Safety Information for Xyrem

WARNING: Taking XYREM with other CNS depressants such as medicines used to make you or your child fall asleep, including opioid analgesics, benzodiazepines, sedating antidepressants, antipsychotics, sedating anti-epileptic medicines, general anesthetics, muscle relaxants, alcohol, or street drugs, may cause serious medical problems, including trouble breathing (respiratory depression), low blood pressure (hypotension), changes in alertness (drowsiness), dizziness (syncope), and death.

XYREM is a form of gamma hydroxybutyrate (GHB). Abuse or misuse of illegal GHB alone or with other drugs that cause changes in alertness (or consciousness) has caused serious side effects. These effects include seizures, trouble breathing (respiratory depression), changes in alertness (drowsiness), coma, and death.

Because of these risks, you have to go through the XYWAV and XYREM REMS to have your or your child's prescription for XYREM filled.

Do not take XYREM if you take or your child takes other sleep medicines or sedatives (medicines that cause sleepiness), drink alcohol, or have a rare problem called succinic semialdehyde dehydrogenase deficiency.

Keep XYREM in a safe place to prevent abuse and misuse. Selling or giving away XYREM may harm others and is against the law. Tell your doctor if you have ever abused or been dependent on alcohol, prescription medicines, or street drugs.

Anyone who takes XYREM should not do anything that requires them to be fully awake or is dangerous, including driving a car, using heavy machinery, or flying an airplane, for at least 6 hours after taking XYREM. Those activities should not be done until you know how XYREM affects you or your child.

XYREM can cause serious side effects, including the following:

- **Breathing problems, including** slower breathing, trouble breathing, and/or short periods of not breathing while sleeping (sleep apnea). People who already have breathing or lung problems have a higher chance of having breathing problems when they use XYREM.
- **Mental health problems,** including confusion, seeing or hearing things that are not real (hallucinations), unusual or disturbing thoughts (abnormal thinking), feeling anxious or upset, depression, or thoughts of killing yourself or trying to kill yourself. Tell your doctor if you or your child have or had depression or have tried to harm yourself. **Call your doctor right away if you have or your child has symptoms of mental health problems.**
- **Sleepwalking.** Sleepwalking can cause injuries. Call your doctor if you or your child starts sleepwalking. Your doctor

should check you or your child.

Tell your doctor if you are or your child is on a salt-restricted diet or if you have or your child has high blood pressure, heart failure, or kidney problems. XYREM contains a lot of sodium (salt) and may not be right for you or your child.

The most common side effects of XYREM include nausea, somnolence, dizziness, vomiting, bedwetting, and tremor (in adults). In pediatric patients, headache, decreased appetite, and weight decrease were also common. Your side effects may increase when you take higher doses of XYREM. XYREM can cause physical dependence and craving for the medicine when it is not taken as directed. These are not all the possible side effects of XYREM.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please find full prescribing information here: http://pp.jazzpharma.com/pi/xyrem.en.USPI.pdf

About Jazz Pharmaceuticals plc

Jazz Pharmaceuticals plc (NASDAQ: JAZZ) is a global biopharmaceutical company whose purpose is to innovate to transform the lives of patients and their families. We are dedicated to developing life-changing medicines for people with serious diseases—often with limited or no therapeutic options. We have a diverse portfolio of marketed medicines and novel product candidates, from early- to late-stage development, in neuroscience and oncology. Within these therapeutic areas, we are identifying new options for patients by actively exploring small molecules and biologics, and through innovative delivery technologies and cannabinoid science. Jazz is headquartered in Dublin, Ireland and has employees around the globe, serving patients in nearly 75 countries. Please visit www.jazzpharmaceuticals.com for more information.

Media Contact:

Kristin Bhavnani
Head of Global Corporate Communications
Jazz Pharmaceuticals plc
CorporateAffairsMediaInfo@jazzpharma.com
Ireland +353 1 637 2141
U.S. +1 215 867 4948

Investors:

Andrea N. Flynn, Ph.D.
Vice President, Head, Investor Relations
Jazz Pharmaceuticals plc
InvestorInfo@jazzpharma.com
Ireland +353 1 634 3211
U.S. +1 650 496 2717

References:

1. Center for Food Safety and Applied Nutrition. Sodium Reduction. U.S. Food and Drug Administration; 2021. Accessed October 2023.
2. National Institute of Neurological Disorders and Stroke. Narcolepsy. https://www.ninds.nih.gov/health-information/disorders/narcolepsy?search-term=narcolepsy%22%20\l%20%22toc-what-is-narcolepsy-. Accessed October 2023.
3. Dauvilliers Y, Arnulf I, Mignot E. Narcolepsy with cataplexy. *Lancet*. 2007;369(9560):499-511.
4. Colten HR, Altevogt BM, Institute of Medicine (US) Committee on Sleep Medicine and Research, eds. *Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem*. Washington (DC): National Academies Press (US); 2006.
5. Peacock J, Benca RM. Narcolepsy: clinical features, co-morbidities & treatment. *Indian Journal of Medical Research*. 2010;131(2):338-349.
6. National Health Service. Narcolepsy – Overview. 2019. https://www.nhs.uk/conditions/narcolepsy/. Accessed October 2023.
7. Ben-Joseph RH, Saad R, Black J, et al. Cardiovascular burden of narcolepsy disease (CV-BOND): a real-world evidence study. Presented at: 2022 AAN Annual Meeting; April 2-7; Seattle, Washington. Poster 1203.
8. Black J, Reaven NL, Funk SE, et al. Medical comorbidity in narcolepsy: findings from the Burden of Narcolepsy Disease (BOND) study. *Sleep Med*. 2017;33:13-18.
9. Ohayon MM, Black J, Lai C, et al. Increased mortality in narcolepsy. *Sleep*. 2014;37(3):439-444.
10. Ohayon MM. Narcolepsy is complicated by high medical and psychiatric comorbidities: a comparison with the general population. *Sleep Med*. 2013;14(6):488-492.
11. Billiard M, Sonka K. Idiopathic hypersomnia. *Sleep Med Rev*. 2016;29:23-33.
12. Trotti LM. Idiopathic hypersomnia. *Sleep Med Clin*. 2017;12(3):331-344.
13. American Academy of Sleep Medicine. The International Classification of Sleep Disorders. Third Edition (ICSD-3). 2014.
14. Khan Z, Trotti LM. Central disorders of hypersomnolence: focus on the narcolepsies and idiopathic hypersomnia. *Chest*. 2015 Jul;148(1):262-273.
15. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fifth Edition (DSM-5). 2020.
16. Jazz Pharmaceuticals, Inc, Data on file. JZP258-2020-047-29 Oct 2020.
17. Evangelista E, Lopez R, Dauvilliers Y. Update on treatment for idiopathic hypersomnia. *Expert Opin Investig Drugs*. 2018;27(2):187-192.
18. Ozaki A, Inoue Y, Hayashida K, et al. Quality of life in patients with narcolepsy with cataplexy, narcolepsy without

cataplexy, and idiopathic hypersomnia without long sleep time: comparison between patients on psychostimulants, drug-naïve patients and the general Japanese population. *Sleep Med*. 2012;13(2):200-206.
19. Jazz Pharmaceuticals, Inc, Data on file.
20. Anderson KN, Pilsworth S, Sharples LD, et al. Idiopathic hypersomnia: a study of 77 cases. *Sleep*. 2007;30(10):1274-1281.
21. Masri TJ, Gonzales CG, Kushida CA. Idiopathic hypersomnia. *Sleep Med Clin*. 2012;7(2):283-289.
22. Trotti LM, Arnulf I. Idiopathic hypersomnia and other hypersomnia syndromes. *Neurotherapeutics*. 2021;18(1):20-31.
23. Xywav (calcium, magnesium, potassium and sodium oxybates) oral solution. Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc. 2021.
24. United States Drug Enforcement Agency. Drug Scheduling. https://www.dea.gov/drug-scheduling. Accessed October 2023.
25. Xyrem (sodium oxybate) oral solution. Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc. 2022.

View original content to download multimedia:https://www.prnewswire.com/news-releases/jazz-pharmaceuticals-presents-data-highlighting-the-continued-need-for-low-sodium-treatment-option-xywav-calcium-magnesium-potassium-and-sodium-oxybates-oral-solution-and-real-world-evidence-based-approaches-for-individuali-301963620.html

SOURCE Jazz Pharmaceuticals plc